MEDICINE CABINETS

Cranberry, feverfew, horse chestnut, and kava

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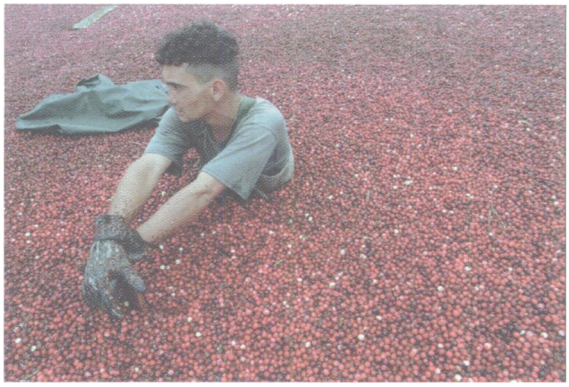
A growing body of controlled clinical trials, primarily from European countries, suggest that many herbal medicines have therapeutic activity with few adverse effects. The quality of these studies is variable. Most clinical trials of herbal medicines have not received the same rigorous level of scientific scrutiny as have drugs that have been approved by the Food and Drug Administration (FDA) in the United States. Dose-response studies are almost nonexistent and few herbal medicines have been compared to standard doses of conventional pharmaceutical drugs. Methodologic study weaknesses, publication bias, and contrasting results of studies contribute to disagreements and skepticism in interpreting herbal literature. The following four herbal medicines (among many others) have potential benefits supported by randomized controlled trials reported in US or European literature.

CRANBERRY (*Vaccinium macrocarpon*)

Long used by patients to help prevent urinary tract infections, cranberry juice was once thought to work by acidifying the urine or by the excretion of hippuric acid. It is now known that specific proanthocyanidins, chemicals found in cranberries (as well as blueberries), inhibit the adherence of *E coli* to urinary tract epithelial cells.[1,2]

Controlled trials

Two preliminary US randomized controlled trials suggest that there may be clinical benefits with cranberry products. In one well-designed, double-blind placebo-controlled study, investigators gave 300 ml/day of cranberry juice cocktail (supplied by Ocean Spray Cranberries, Inc.) or a placebo beverage to 153 elderly female nursing home residents over a 6-month period.[3] Pyuria with bacteriuria was significantly reduced in the cranberry (15%) versus placebo (28.1%) group (P=0.004). Antibiotics for urinary tract infections were prescribed eight times in the cranberry group and 16 times in the placebo group by the patients' own physicians.



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Cranberries

In a much smaller double-blind placebo-controlled trial, with a crossover design over 6 months, investigators gave a daily cranberry extract capsule (supplied by Solaray, Inc.) or a placebo to 19 young, sexually active women (median age 37) with recurrent urinary tract infections.[4] Nine people were lost to follow-up due to pregnancy, moving out of the area, or other infections requiring antibiotics. Of the remaining 10 patients, while taking the cranberry product, seven had reduced frequency of clinical urinary tract infections, one person had one more urinary tract infection, and two people had no change in their frequency of infection. Of 21 incidents of urinary tract infections, 6 occurred while taking the cranberry product and 15 occurred while taking placebo, a statistically significant difference (P<0.005).

Adverse effects and administration

There are no known adverse effects of cranberries. Doses in the clinical trials included 300 ml/day of a standard cranberry juice cocktail beverage, in single or divided doses, or a daily 400-mg dietary supplement capsule.

Conclusion

Physicians can consider cranberry products to be a safe prophylactic therapy that may help reduce the frequency of urinary tract infections in susceptible individuals. Cranberry's prophylactic activity compared to antimicrobial drugs and cranberry's effects on acute urinary infections have not been investigated.

FEVERFEW (*Tanacetum parthenium*)

Commonly used for headaches, feverfew has also been used for arthritis, menstrual discomfort, and a variety of other disorders. Pharmacologically, feverfew may inhibit prostaglandin synthesis and histamine release from mast cells, affect platelet activity, and/or inhibit vascular smooth muscle contractility.[5,6]

Controlled trials

Four randomized controlled trials from outside the United States have studied feverfew for the prophylaxis of migraine headaches; three of those studies found beneficial results compared to placebo. In a small British double-blind placebo-controlled study, investigators studied 17 patients who regularly ate feverfew leaves for self-prophylaxis of migraines.[7] Switching patients to a placebo caused a significant increase in migraine symptoms compared to symptoms in patients who continued with a feverfew capsule preparation. Other British investigators randomized 76 migraine patients in a double-blind placebo-controlled study with a crossover design lasting 8 months.[8] Feverfew (70- to 114-mg/capsule of powdered dry leaf daily) significantly decreased the num-

ber of attacks (3.6 vs 4.7 attacks/2-month period, P<0.005) and decreased symptoms of nausea and vomiting compared to a placebo (P<0.02). There was a nonsignificant trend toward milder headaches (P=0.06), and the duration of individual attacks was not reduced. However, 16 patients did not complete the study, which was not taken into account with intention-to-treat analysis. An Israeli double-blind placebo-controlled crossover trial of 57 migraine patients, lasting 4 months, demonstrated that feverfew (100-mg capsule of powdered dry leaf daily) significantly decreased pain, vomiting, and sensitivity to light and noise compared to a placebo (P<0.01).[9]

In contrast, a Dutch randomized double-blind placebo-controlled crossover study found that feverfew in a dose of 143 mg/day was no better than a placebo.[10] Fifty migraine patients took a specific ethanolic feverfew extract (as opposed to powdered dry leaf) that was standardized to parthenolide. This chemical was previously considered to be an active component of feverfew but had never been confirmed clinically. The negative findings of this study may be the result of standardizing to the wrong chemical entity, as parthenolide may not be the active constituent. None of the three crossover studies had adequate washout periods.

In a separate double-blind placebo-controlled study, using a dose of 70- to 86-mg/day of encapsulated dried leaf, feverfew was found to be ineffective for the treatment of rheumatoid arthritis.[11]

Adverse effects and administration

Feverfew use is associated infrequently with mouth ulceration or inflammation, mild gastrointestinal disturbances, and contact allergy to the plant,[6] but reported side effects from the clinical trials were no different than placebo. The feverfew plant can cause abortions in cattle and is therefore contraindicated during pregnancy.[6] Feverfew may affect platelet activity in vitro, but there have been no reported cases of laboratory abnormalities, bleeding, or adverse interactions with anticoagulant or antiplatelet drugs. The dose used in successful controlled trials was approximately 50 to100 mg QD of encapsulated dried leaf preparations.

Conclusion

Physicians can consider feverfew to be a relatively safe herbal medicine that may be beneficial for migraine headache prophylaxis. Feverfew has not been compared to standard pharmacologic prophylaxis in controlled trials, nor has it been investigated or is it recommended for treatment of acute migraine attacks.

HORSE CHESTNUT (*Aesculus hippocastanum*)

Traditionally used for arthritis and rheumatic complaints, a standardized horse chestnut seed extract is extremely popular and has been well-studied in Europe for treating chronic venous insufficiency. It has also been promoted as a topical treatment for varicose veins and hemorrhoids. Horse chestnut seed extract has been shown to decrease venous capillary permeability in pharmacologic studies.[12,13]

Controlled trials

A recent systematic review of worldwide literature found 13 randomized controlled trials, all double-blinded, that fulfilled a majority of standard inclusion criteria to reduce bias.[12] None of these trials, however, was completely flawless. Eight studies were placebo-controlled and five were controlled against another European phytotherapy agent. Studies lasted between 2 and 12 weeks. In all eight placebo-controlled studies, horse chestnut seed extract significantly decreased the symptoms of chronic venous insufficiency (leg pain, pruritus, feeling of leg fatigue or tenseness) or decreased leg volume and edema, compared to placebo (P-values all <0.05). Although not adequately blinded, one study found horse chestnut seed extract to have similar benefits to compression stockings.[14]

Adverse effects and administration

Ingestion of high doses or parenteral administration of horse chestnut preparations may be toxic; renal, hepatic, and hematologic abnormalities have been reported rarely.[15] The side effects of the processed extract are generally similar to placebo, however, with reports of mild gastrointestinal symptoms, headache, dizziness, and pruritus in less than 3% of patients.[12] Standardized horse chestnut seed extract contains 16% to 20% triterpene glycosides, calculated as aescin (or escin), which is considered the main active constituent. The usual recommended daily dose is 100 to 150 mg of aescin equivalent, or about 500 to 750 mg of horse chestnut seed extract that contains 20% aescin. In the clinical trials, the most common dose was 50 mg of aescin (about 250 mg of horse chestnut seed extract) bid, using a commercial preparation that is now marketed in the United States (Venostat, by Pharmaton/Boehringer Ingelheim).

Conclusion

Horse chestnut seed extract is a safe herbal medicine that may be useful for the treatment of chronic venous insufficiency. Benefits have not been adequately compared to standard therapies such as compression stockings or diuretics, but there is little reason why it cannot be tried as an adjunctive or alternative therapy.

KAVA (*Piper methysticum*)

A beverage made from the root of the kava plant has been used for centuries by South Pacific islanders as an integral part of their culture, both ceremonially and socially, with relaxing or calming properties.[16] Specific kava extracts have been studied in Europe and are widely marketed in solid dosage forms to treat symptoms of anxiety, stress, or ten-

sion, without causing cognitive disturbances. The active constituents, kava pyrones (also called kava lactones), have experimentally been found to have skeletal muscle relaxant, anticonvulsant, and local anesthetic properties.[13,16]

Controlled trials

Five randomized double-blind placebo-controlled trials of kava extract products have been published in Europe.[17-21] Studies included 40 to 100 patients each and lasted from 1 to 6 months. Two studies included women with primarily perimenopausal complaints, while the others included patients with a variety of different anxiety disorders. All studies, using several objective anxiety rating tools, found that kava reduced anxiety symptoms compared to placebo. Effects were usually observed within one week (the first measurement point in the studies), but the longest trial found effects to be statistically significant only after 2 months.[21] After 6 months, withdrawal effects were reportedly not observed when therapy was discontinued after a one-week placebo washout. One European randomized double-blind comparative trial of 172 patients found beneficial results similar to that of relatively low-dose benzodiazepines (oxazepam 15 mg/day and bromazepam 9 mg/day).[17,22]

A separate randomized double-blind placebo-controlled trial conducted with a US dietary supplement (Kavatrol, by Natrol) studied kava's effects on mild day-to-day stress for one month in 60 patients. The investigators report beneficial effects, but results are currently published only in abstract form.[23]

Adverse effects and administration

Mild side effects such as gastrointestinal discomfort, headache, dizziness, and allergic skin reactions have been reported in less than 2.3% of patients in open studies and were generally similar to placebo in the controlled trials.[13] A variety of studies using EEG and psychometric tests suggest that European kava preparations, unlike benzodiazepines, do not affect intellectual and motor functioning.[13,24,25] A kava dermopathy characterized by yellowing of the skin and scaly dermatitis is common in chronic heavy kava drinkers in the South Pacific; the effects are reversible after discontinuation of the herb.[26]

A few serious adverse effects have been occasionally associated with kava use. Traditionally prepared kava beverages, especially with excessive doses, may produce an effect similar to depression of the central nervous system.[27,28] One 44-year-old US motorist was arrested for intoxication after appearing to be drunk, but with no evidence of alcohol use, presumably after drinking 16 cups of a kava beverage.[29] There are three reports of extrapyramidal-like dystonic reactions and one case of worsening Parkinson's disease, mostly from European kava preparations.[30,31] Severe disorientation has been reported in a patient using a US kava supplement in conjunction with alprazolam and cimetidine.[32]

The usual therapeutic dose of kava is about 140 to 250 mg/day of the kava pyrone constituents, in 2 to 3 divided doses. In the US clinical trial, two tablets containing 60 mg each (120 mg kava pyrones total) were given twice a day. In the European clinical trials, the usual dose was 70 mg three times a day of kava pyrones (100 mg tid of a specific extract product). This European product (WS 1490) is manufactured according to strict guidelines and is usually standardized to include 70% kava pyrones. In contrast, US supplements vary widely among brands, with kava pyrone content usually between 30% and 55%. Consumers should read the labels carefully.

Conclusion

Kava may be a beneficial herbal medicine for mild stress or anxiety, with minimal abuse potential. However, the potential for adverse effects from doses higher than recommended and drug interactions are concerning. The relative efficacy of kava compared to usual doses of standard antianxiety drugs is not known. Kava is contraindicated in patients with Parkinson's disease. It would also be prudent, until effects are better known, to avoid kava in patients taking drugs with extrapyramidal side effects or who are taking central nervous system depressants such as benzodiazepines or alcohol.

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Echinacea in the treatment and prevention of upper respiratory tract infections

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Introduction

An estimated $21.2 billion was spent on complementary medicine in 1997.[1] Echinacea, the top-selling herbal product in the United States, is at the forefront of the herbal revolution, with annual sales estimated at more than $300 million. The German Commission E lists that echinacea preparations "support and promote the natural powers of resistance of the body, especially in infectious conditions of the nose and throat."[2]

The objective of this analysis is to describe the pharmacology and clinical evidence for echinacea in the treatment and prevention of upper respiratory tract infections.

Historical use

Extracts, teas, tinctures, tonics, tablets, and ointments containing various parts of the echinacea plant (family Compositae) have been used since the 1600s by Native Americans. Tribes including the Cheyenne and the Crow used echinacea for a variety of medical problems, from sore gums and coughs to bowel trouble and snakebites.[3] The popularity of echinacea as a general medical treatment did not occur until the late 1800s, when Nebraska physician H.C.F. Meyer sold a root extract of *Echinacea angustifolia* as a "blood purifier."[4,5] Meyer subsequently sent his herbal concoction to John King and John Lloyd, a prominent physician/pharmacist team involved in the eclectic medicine movement of the late 1800s. Soon Lloyd Brothers Pharmacists of Cincinnati began marketing echinacea extracts as "anti-infective agents."[3-5] The popularity of echinacea extracts remained steady through the early part of this century, and from 1916 to 1950 echinacea was included in the US National Formulary. In the 1930s, with the advent of the sulfa antibiotics, the popularity of echinacea as an anti-infective agent began to wane in the United States, and only in the past few decades has it made a comeback.

Recent clinical studies of echinacea have focused on the treatment and prevention of upper respiratory infections. Other suggested uses include alleviation or reduction of adverse effects of chemotherapeutic agents; treatment of urinary tract infections; and topical use for chronic wounds, snake and mosquito bites, and recurrent *Candida* infections.[6]

Botany and taxonomy

The word "echinacea" is derived from the Greek *echinos,* meaning "hedgehog" or "sea urchin." The name was given to the plant because of its spiky seed heads.[4] The three most common echinacea species for medicinal purposes are *E angustifolia* (narrow-leaved), *E purpurea* (common), and *E pallida* (pale). *E purpurea* is the most popular commercially cultivated species. Common names for these perennial herbs include purple coneflower, Missouri snakeroot, Indianhead, scurvy root, comb flower, hedgehog, and red sunflower.[3-7] Native to Kansas, Nebraska, and Missouri, echinacea is closely related to sunflowers, daisies, and ragweed, all members of the Compositae/Asteraceae family. The stems have a sharp tingling taste when chewed.[8] Medicinal products are prepared from the dried roots of *E angustifolia* and *E pallida,* and from the juice of the stems and flowers as well as the root of *E purpurea.*[3,6,7]

Chemistry and pharmacology

As with many medicinal plants, echinacea contains at least six distinct chemical constituents with pharmacologic activity (polysaccharides, flavonoids, chicoric acid glycosides, essential oils, polyacetylenes, and alkylamides).[3-7] There is much controversy and confusion over which